

WHAT IS CLAIMED:

1. A method for attenuating an immune response in a subject, comprising:
placing at least a portion of a lead comprising an electrode within a tissue of the
subject at a location in which stimulation of the tissue by the electrode is
capable of stimulating a sympathetic neuron;
applying an electrical stimulation pulse to the tissue via the electrode to stimulate
the sympathetic neuron in an amount effective to attenuate an immune
response.
2. The method of claim 1, wherein a plurality of electrical pulses are applied to the
tissue.
3. The method of claim 1, further comprising implanting a pulse generator within
the subject, wherein the pulse generator produces the electrical stimulation pulse
and is electrically coupled to the electrode.
4. The method of claim 1, wherein the electrode is placed in contact with the
sympathetic neuron.
5. The method of claim 1, wherein the sympathetic neuron is a neuron selected from
the group consisting of:
a projection from the brain to the spinal cord, an interneuron, a pre-ganglionic
neuron, a ganglion, and a post-ganglionic neuron.
6. The method of claim 5, wherein the sympathetic neuron is a post-ganglionic
neuron.
7. The method of claim 6, wherein the sympathetic neuron is a neuron of the splenic
nerve.

8. The method of claim 4, wherein the sympathetic neuron is a neuron of the splenic nerve.
9. The method of claim 1, wherein the sympathetic neuron is a neuron of the splenic nerve.
10. The method of claim 1, wherein the electrode is placed in contact with an end organ.
11. The method of claim 10, wherein the end organ is a lymph organ.
12. The method of claim 11, wherein the lymph organ is a spleen.
13. The method of claim 1, wherein the electrode is placed in contact with tissue of an organ in a peritoneal sac.
14. The method of claim 13, wherein the organ in the peritoneal sac is selected from the group consisting of:
pancreas, stomach, and intestine.
15. The method of claim 1, wherein the immune response is an inflammatory immune response.
16. The method of claim 1, wherein the cell is in a patient suffering from, or at risk for, a disease or disorder mediated by an immune response.
17. The method of claim 16, wherein the disease or disorder is selected from the group consisting of appendicitis, peptic, gastric and duodenal ulcers, peritonitis, pancreatitis, pseudomembranous colitis, acute ulcerative colitis, chronic ulcerative colitis and ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, nosocomial infection, Crohn's disease,

inflammatory bowel disease, enteritis, Whipple's disease, diabetes, asthma, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, cystic fibrosis, pneumonitis, pelvic inflammatory disease, , alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, herpes infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, urticaria, warts, wheals, vasculitis, cardiovascular disease, angiitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, rheumatoid arthritis, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome, meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillane-Barre syndrome, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, Sjogren's syndrome, myasthenia gravis, thyroiditis, systemic lupus erythematosus, lupus erythematosus, Addison's disease, pernicious anemia, Goodpasture's syndrome, Behcet's syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Type I diabetes, ankylosing spondylitis, spinal cord injury, Retier's syndrome, Graves disease, and Hodgkins disease

18. The method of claim 2, further comprising:
sensing a condition, and
modifying a parameter of at least one of the plurality of electrical pulses based on the sensed condition.

19. The method of claim 18, wherein sensing the condition comprises detecting a characteristic or symptom associated with a disorder or disease associated with an immune response or stimulation of the one or more neurons.
20. The method of claim 19, wherein the characteristic or symptom is selected from the group consisting of presence of an immune mediator, an amount of an immune mediator, an objective symptom of the subject.
21. The method of claim 20, wherein the immune mediator is a cytokine receptor.
22. The method of claim 21, wherein the cytokine receptor is selected from the group consisting of TNF receptor, IL-1b receptor, and Toll-like receptors.
23. The method of claim 22, wherein the immune mediator is a chemokine.
24. The method of claim 23, wherein the chemokine is selected from the group consisting of 6Ckine and MIP3beta.
25. The method of claim 20, wherein the immune mediator is a chemokine receptor.
26. The method of claim 25, wherein the chemokine receptor is CCR7 receptor.
27. The method of claim 20, wherein the immune mediator is a cell type involved in an immune response.
28. The method of claim 27, wherein the cell type is selected from the group consisting of Langerhans cell, dendritic cell, T lymphocyte, and B lymphocyte.
29. The method of claim 20, wherein the immune mediator is a cell surface molecule involved in an immune response.

30. The method of claim 29, wherein the cell surface molecule is selected from the group consisting of major histocompatibility complex (MHC), CD80, CD86, CD28, CD40.
31. The method of claim 20, wherein the immune mediator is an exogenous antigen.
32. The method of claim 31, wherein the exogenous antigen is selected from the group consisting of a bacterial antigen, a viral antigen, and a fungal antigen.
33. The method of claim 20, wherein the immune mediator is a cytokine.
34. The method of claim 34, wherein the cytokine is a pro-inflammatory or anti-inflammatory cytokine.
35. The method of claim 34, wherein the cytokine is selected from the group consisting of tumor necrosis factor alpha (TNF α), interleukin (IL)-1 α , IL-1 β , IL-5, IL-6, IL-8, IL-18, interferony, platelet –activating factor (PAF), macrophage migration inhibitory factor (MIF), high mobility group box protein 1 (HMGB-1), IL-4, IL-10, IL-13, and IL-17.
36. The method of claim 18, wherein the condition is the presence or amount of transforming growth factor (TGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), fibroblast growth factor (FGF), intracellular adhesion molecule (I-CAM), subtypes thereof, or nitric oxide.
37. The method of claim 18, wherein at least one of the one or more conditions is the presence or amount of nuclear factor kappa B (NF κ -B), early growth response protein (ERG-1), a mitogen-activated protein (MAP) kinase, toll-like receptors (TLRs), or a SMAD transcription factor.

38. The method of claim 18, wherein the condition is selected from the group consisting of white blood cell count, body temperature, degree of swelling, degree of flushing, pain tolerance, and electrical activity of the subject's heart.
39. The method of claim 18, wherein sensing the condition comprises detecting a condition associated with stimulation of a sympathetic neuron.
40. The method of claim 39, wherein the sensing the condition comprises detecting a membrane potential of a neuron.
41. The method of claim 36, wherein the sensing the condition comprises detecting a frequency with which the stimulated neuron undergoes an action potential.
42. The method of claim 39, the sensing the condition comprises detecting a sympathetic neurotransmitter, or metabolite thereof.
43. A system for attenuating an immune response in a subject, comprising:
a medical device capable of stimulating one or more sympathetic neuron of the
subject; and
operator instructions indicating that the medical device may be used to stimulate
one or more neurons associated with a sympathetic nervous system to
attenuate an immune response.
44. The system of claim 43 further comprising instructions for operating the medical
device to stimulate a splenic nerve of the subject.
45. The system of claim 43 further comprising one or more sensor coupled to the
medical device, wherein the sensor is capable of detecting a condition associated
with stimulation of one or more neurons associated with a sympathetic nervous
system, associated with attenuation of an immune response, or both.

46. The system of claim 43, wherein the medical device comprises a neurostimulator.
47. The system of claim 46, wherein the neurostimulator is an implantable pulse generator.
48. The system of claim 43, wherein the medical device comprises a drug pump.
49. The system of claim 43, wherein the drug pump is implantable.
50. The system of claim 48, wherein the medical device further comprises a reservoir coupled to the drug pump.
51. The system of claim 49, wherein the operator instructions further indicate that a therapeutic agent may be housed in the reservoir.
52. The system of claim 51, wherein the therapeutic agent is selected from the group consisting of an agonist of a stimulator neurotransmitter receptor, antagonist of an inhibitory neurotransmitter receptor, agonists of receptors of neurotransmitters of a sympathetic nervous system.
53. The system of claim 51, wherein therapeutic agent is selected from the group consisting of a glutamate agonist, a GABA antagonist, a beta-adrenergic agonist, an alpha-adrenergic antagonist, a dopamine agonist, a substance P agonist, and a neuropeptide Y agonist.
54. A method for inhibiting release of a proinflammatory cytokine from a cell in a mammalian subject, comprising:
placing at least a portion of a lead comprising an electrode within a tissue of the mammalian subject at a location in which stimulation of the tissue by the electrode is capable of stimulating a sympathetic neuron; and

applying an electrical stimulation pulse to the tissue via the electrode to stimulate the sympathetic neuron in an amount effective to inhibit release of the proinflammatory cytokine from the cell.

55. The method of claim 54, wherein a plurality of electrical pulses are applied to the tissue.
56. The method of claim 54, further comprising implanting a pulse generator within the subject, wherein the pulse generator produces the electrical stimulation pulse and is electrically coupled to the electrode.
57. The method of claim 54, wherein placing the lead comprises placing the electrode in contact with the sympathetic neuron.
58. The method of claim 54, wherein the sympathetic neuron is a neuron selected from the group consisting of a projection from the brain to the spinal cord; an interneuron; a pre-ganglionic neuron; a ganglion; and a post-ganglionic neuron.
59. The method of claim 58, wherein the sympathetic neuron is a post-ganglionic neuron.
60. The method of claim 59, wherein the sympathetic neuron is a neuron of the splenic nerve.
61. The method of claim 60, wherein the sympathetic neuron is a neuron of the splenic nerve.
62. The method of claim 54, wherein the sympathetic neuron is a neuron of the splenic nerve.

63. The method of claim 54, wherein placing the lead comprises placing the electrode in contact with an end organ.
64. The method of claim 63, wherein the end organ is a lymph organ.
65. The method of claim 64, wherein the lymph organ is a spleen.
66. The method of claim 54, wherein placing the lead comprises placing the electrode in contact with tissue of an organ in a peritoneal sac.
67. The method of claim 66, wherein the organ in the peritoneal sac is selected from the group consisting of pancreas; stomach; and intestine.
68. The method of claim 54, wherein the proinflammatory cytokine is selected from the group consisting of tumor necrosis factor alpha (TNF α); interleukin (IL)-1 α ; IL-1 β ; IL-5; IL-6; IL-8; IL-18; interferony, platelet-activating factor (PAF); macrophage migration inhibitory factor (MIF); and high mobility group protein 1 (HMG-1).
69. The method of claim 54, wherein the proinflammatory cytokine is selected from the group consisting of TNF- α ; IL-1; and IL-6.
70. The method of claim 54, wherein the proinflammatory cytokine is TNF- α .
71. A method for inhibiting release of one or more proinflammatory cytokines from one or more cells in a mammalian subject, comprising:
placing at least a portion of a first lead comprising a first electrode within a first tissue of the subject at a location in which stimulation of the first tissue by the first electrode is capable of stimulating a sympathetic neuron;
placing at least a portion of a second lead comprising a second electrode within a second tissue of the subject at a location in which stimulation of the

- second tissue by the second electrode is capable of stimulating a parasympathetic neuron;
- applying a first electrical stimulation pulse to the first tissue via the first electrode to stimulate the sympathetic neuron in an amount effective to inhibit release of at least one of the one or more proinflammatory cytokines from at least one of the one or more cells; and
- applying a second electrical stimulation pulse to the second tissue via the second electrode to stimulate the parasympathetic neuron in an amount effective to inhibit release of at least one of the one or more proinflammatory cytokines from at least one of the one or more cells.
72. The method of claim 71, wherein the first lead and the second lead are the same lead.
73. The method of claim 71, wherein the sympathetic neuron is a neuron of the splenic nerve.
74. The method of claim 71, wherein the parasympathetic neuron is a neuron of the vagus nerve.
75. The method of claim 74, wherein the sympathetic neuron is a neuron of the splenic nerve.
76. A system for inhibiting release of a proinflammatory cytokine from a cell of a mammalian subject, comprising:
a medical device capable of stimulating one or more sympathetic neuron of the subject; and
operator instructions indicating that the medical device may be used to stimulate one or more neurons associated with a sympathetic nervous system to inhibiting release of a proinflammatory cytokine.

77. The system of claim 76, further comprising instructions for operating the medical device to stimulate a splenic nerve of the subject.
78. A method for inducing release of an anti-inflammatory cytokine from a mammalian cell, comprising:
placing at least a portion of a lead comprising an electrode within a tissue of the subject at a location in which stimulation of the tissue by the electrode is capable of stimulating a sympathetic neuron;
applying an electrical stimulation pulse to the tissue via the electrode to stimulate the sympathetic neuron in an amount effective to induce release of the anti-inflammatory cytokine.
79. The method of claim 78, wherein a plurality of electrical pulses are applied to the tissue.
80. The method of claim 78, further comprising implanting a pulse generator within the subject, wherein the pulse generator produces the electrical stimulation pulse and is electrically coupled to the electrode.
81. The method of claim 78, wherein the electrode is placed in contact with the sympathetic neuron.
82. The method of claim 78, wherein the sympathetic neuron is a neuron selected from the group consisting of:
a projection from the brain to the spinal cord, an interneuron, a pre-ganglionic neuron, and a post-ganglionic neuron.
83. The method of claim 82, wherein the sympathetic neuron is a post-ganglionic neuron.

84. The method of claim 83, wherein the post-ganglionic neuron is a neuron of the splenic nerve.
85. The method of claim 84, wherein the sympathetic neuron is a neuron of the splenic nerve.
86. The method of claim 78, wherein the sympathetic neuron is a neuron of the splenic nerve.
87. The method of claim 78, wherein the electrode is placed in contact with an end organ.
88. The method of claim 87, wherein the end organ is a lymph organ.
89. The method of claim 88, wherein the lymph organ is a spleen.
90. The method of claim 78, wherein the electrode is placed in contact with tissue of an organ in a peritoneal sac.
91. The method of claim 90, wherein the organ in the peritoneal sac is selected from the group consisting of:
pancreas, stomach, and intestine.
92. The method of claim 78, wherein the anti-inflammatory cytokine is selected from the group consisting of IL-4, IL-10, IL-17, IL-13, IL-1alpha, and TNFalpha receptor.
93. The method of claim 78, wherein the anti-inflammatory cytokine is IL-10.
94. A method for inducing release of one or more anti-inflammatory cytokines from one or more cells in a mammalian subject, comprising:

placing at least a portion of a first lead comprising a first electrode within a first tissue of the subject at a location in which stimulation of the first tissue by the first electrode is capable of stimulating a sympathetic neuron;
placing at least a portion of a second lead comprising a second electrode within a second tissue of the subject at a location in which stimulation of the second tissue by the second electrode is capable of stimulating a parasympathetic neuron;
applying a first electrical stimulation pulse to the first tissue via the first electrode to stimulate the sympathetic neuron in an amount effective to induce release of at least one of the one or more anti-inflammatory cytokines from at least one of the one or more cells; and
applying a second electrical stimulation pulse to the second tissue via the second electrode to stimulate the parasympathetic neuron in an amount effective to induce release of at least one of the one or more anti-inflammatory cytokines from at least one of the one or more cells.

- 95. The method of claim 94, wherein the first lead and the second lead are the same lead.
- 96. The method of claim 94, wherein the sympathetic neuron is a neuron of the splenic nerve.
- 97. The method of claim 94, wherein the parasympathetic neuron is a neuron of the vagus nerve.
- 98. The method of claim 97, wherein the sympathetic neuron is a neuron of the splenic nerve.
- 99. A system for inducing release of an anti-inflammatory cytokine from a cell of a mammalian subject, comprising:

a medical device capable of stimulating one or more sympathetic neuron of the subject; and
operator instructions indicating that the medical device may be used to stimulate one or more neurons associated with a sympathetic nervous system to inducing release of an anti-inflammatory cytokine.

100. The system of claim 99, further comprising instructions for operating the medical device to stimulate a splenic nerve of the subject.
101. A method comprising:
quantifying one or more conditions of a subject to establish a health state of the subject, the one or more condition being associated with an immune response;
stimulating one or more neurons of the subject's sympathetic nervous system with a set of stimulation parameters designed to stimulate the one or more neurons at a stimulation level;
determining whether the health state of the subject improved based on changes in one or more of the one or more conditions;
modifying the stimulation parameters based the determination of whether the health state of the subject improved.
102. The method of claim 101, wherein modifying the stimulation parameters comprises increasing the stimulation level if the subject's health state has not improved.
103. The method of claim 101, wherein modifying the stimulation parameters comprises decreasing the stimulation level if the subject's health state has improved.

104. The method of claim 103, further comprising determining whether the subject's health state has regressed; and increasing the stimulation level if the subject's health state has regressed.
105. The method of claim 101, wherein at least one of the one or more the conditions is selected from the group consisting of presence of an immune mediator, an amount of an immune mediator, an objective symptom, and the subject's perception.
106. The method of claim 105, wherein the immune mediator is a cytokine.
107. The method of claim 106, wherein the cytokine is a pro-inflammatory or anti-inflammatory cytokine.
108. The method of claim 106, wherein the cytokine is selected from the group consisting of tumor necrosis factor alpha (TNF α), interleukin (IL)-1 α , IL-1 β , IL-5, IL-6, IL-8, IL-18, interferony, platelet –activating factor (PAF), macrophage migration inhibitory factor (MIF), high mobility group protein 1 (HMG-1), IL-4, IL-10, IL-13, and IL-17.
109. The method of claim 101, wherein at least one of the one or more conditions is the presence or amount of transforming growth factor (TGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), fibroblast growth factor (FGF), intracellular adhesion molecule (I-CAM), subtypes thereof, or nitric oxide.
110. The method of claim 101, wherein at least one of the one or more conditions is the presence or amount of nuclear factor kappa B (NF κ -B), early growth response protein (ERG-1), a mitogen-activated protein (MAP) kinase, or a SMAD transcription factor.

- 111. The method of claim 107, wherein the objective symptom is selected from the group consisting of white blood cell count, body temperature, degree of swelling, degree of flushing, pain tolerance, and electrical activity of the subject's heart.
- 112. The method of claim 101, wherein stimulating the one or more sympathetic neurons comprises directly stimulating the one or more sympathetic neurons.
- 113. The method of claim 112, wherein the one or more sympathetic neuron directly stimulated comprises a projection from the brain to the spinal cord, an interneuron, a pre-ganglionic neuron, a ganglion, or a post-ganglionic neuron.
- 114. The method of claim 113, wherein a post-ganglionic neuron is directly stimulated.
- 115. The method of claim 114, wherein splenic nerve is directly stimulated.
- 116. The method of claim 112, wherein the splenic nerve is indirectly stimulated.
- 117. The method of claim 101, wherein stimulating the one or more sympathetic neurons comprises indirectly stimulating the one or more sympathetic neurons.
- 118. The method of claim 117, wherein the splenic nerve is indirectly stimulated.
- 119. The method of claim 117, wherein an end organ is directly stimulated.
- 120. The method of claim 119, wherein the end organ is a lymph organ.
- 121. The method of claim 120, wherein the lymph organ is the spleen.
- 122. The method of claim 117, wherein an organ of the subject's peritoneal sac is stimulated.

123. The method of claim 112, wherein the organ is selected from the group consisting of pancreas, stomach, and intestine.
124. A computer-readable medium comprising instructions that cause a programmable processor to:
 - quantify one or more conditions of a subject to establish a health state of the subject, the one or more condition being associated with an immune response;
 - instruct a medical device to provide a stimulatory signal having stimulation parameters to a neuron;
 - determine whether the health state of the subject improved based on changes in one or more of the one or more conditions; and
 - modify the stimulation parameters based the determination of whether the health state of the subject improved.
125. A medical device comprising the computer-readable medium of claim 124.
126. The medical device of claim 125, wherein the medical device comprises a pulse generator.
127. The medical device of claim 126, wherein the pulse generator is implantable.
128. The medical device of claim 125, wherein the medical device comprises a drug pump.
129. The medical device of claim 128, wherein the drug pump is implantable.